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# Studies on the Alkaloids of *Thalictrum Thunbergii* DC. (XVI)*

## O-Methylthalicberine 7

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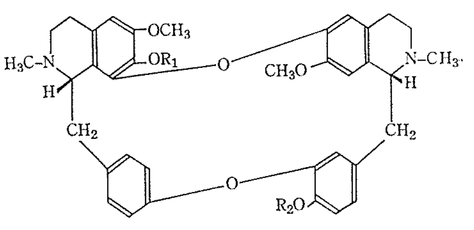
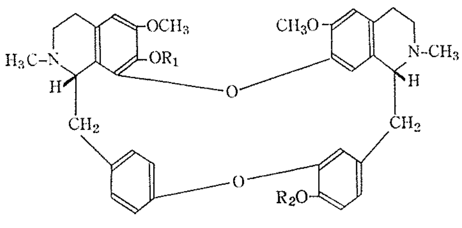
Another evidence that the oxygen of the diphenyl ether linkage was attached to the position 6 of the isoquinoline moiety in the right-hand benzylisoquinoline of O-methyl-thalicberine (**6**) was presented. The investigations on L-N-methyl-O,O-diethylisococlaurine (**9**) and D-N-methyl-O,O-diethylcoclaurine (**14**) were carried out.

In the preceeding paper[1)], we clarified that structures **1** and **2** postulated for thalicrine and homothalicrine, respectively, were incorrect and thalicrine must be aromoline (**3**) itself, accordingly, that the name "homothalicrine" should be changed to "homoaromoline", to which structure **4** should be assigned. These alkaloids belong to the known oxyacanthine type.

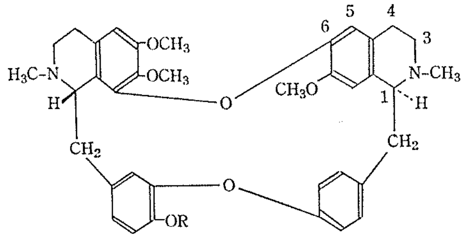
Thalicberine (**5**) and O-methylthalicberine (**6**) remain as the unique bisbenzyl-isoquinoline alkaloids which contain a characteristic type of diphenyl ether linkage. Up to date, several evidences supporting the unique linkage have been presented.[2,3,4,5,6)] In this paper, another strong evidence is presented.



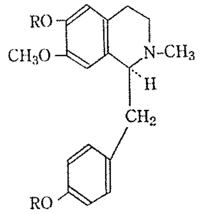
1 : $R_1=R_2=H$
2 : $R_1=H$, $R_2=CH_3$



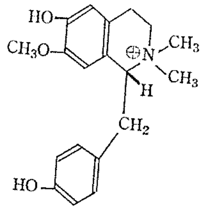
3 : $R_1=R_2=H$
4 : $R_1=H$, $R_2=CH_3$
15 : $R_1=R_2=C_2H_5$



5 : $R=H$
6 : $R=CH_3$



7 : $R=H$
9 : $R=C_2H_5$



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* Part XV: *Bull. Inst. Chem. Res. Kyoto Univ.*, **42,** 235 (1964).
*2 藤田栄一, 冨士　薫, 鈴木豊子

It has been proved that a phenolic bisected base obtained from O-methylthalicberine (**6**) by the cleavage with sodium in liquid ammonia was *d*-L-N-methylisococlaurine (**7**).

Recently, Furukawa *et al.*[7] isolated a new quaternary base, named lotusine, from Lien Tze Hsin (embryo of *Nelumbo nucifera* GAERTN.) of Formosan and Hong-Kong market, and proposed structure **8** to the alkaloid. The methiodide of compound **7** should correspond to the antipode of lotusine iodide.

Now, we carried out again the cleavage of O-methylthalicberine (**6**) with sodium in liquid ammonia, and prepared the methiodide of the resulting phenolic basic product. The compound has the same melting point, that is, m.p. 202-204° (decomp.), as lotusine iodide. The infrared spectra of both compounds in KBr were superimposable as shown in Fig. 1. The melting point of the methiodide was

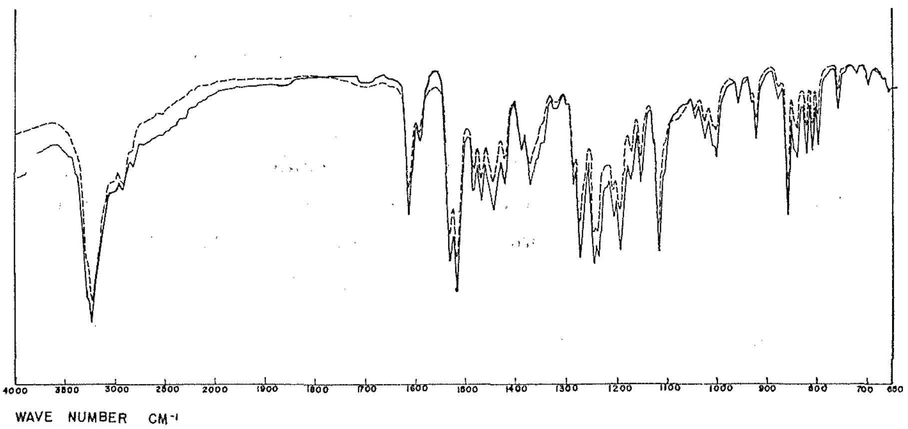



Fig. 1. I.R. Spectra (KBr)
—— Methiodide of Compound 7. (m.p. 202-204°, dec.)
- - - - Lotusine Iodide (m.p. 202-204°, dec.)

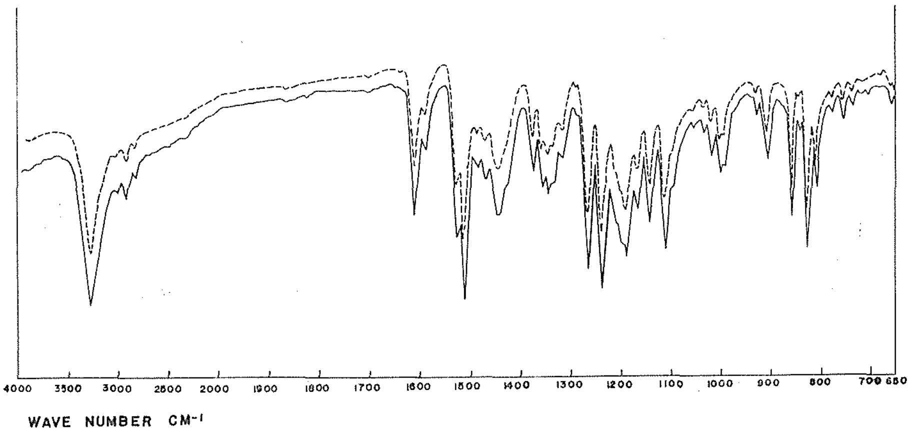



Fig. 2. I.R. Spectra (KBr)
—— Methiodide of Compound 7. (m.p. 221-223°, dec.)
- - - - Lotusine Iodide (m.p. 221-223°, dec.)

raised to 221-223° (decomp.), when recrystallized from ethanol after drying over anhydrous phosphoric acid in a vacuum at 70°. The compound showed $[\alpha]_D+8.9°$. The sample of lotusine iodide also exhibited the same change of the melting point, when treated in the same way. The infrared spectra of both crystals were completely identical, as shown in Fig. 2.

Subsequently, the phenolic base **7** was ethylated with diazoethane. As the resulting non-phenolic product resisted to crystallize, it was converted to the oxalate which corresponds to L-N-methyl-O,O-diethylisococlaurine (**9**) oxalate. As a result of a detailed investigation, it was found that the oxalate has m.p. 146-148° and $[\alpha]_D+3.1°$, and the melting point 181-183° reported for the same compound in the preceeding paper[1] was incorrect.

Recently, Tomita and Ibuka[8] synthesized D,L-N-methyl-O,O-diethylisococlaurine, but the latter resisted to crystallize. So, they prepared its oxalate having m.p. 174°.

A comparison of the N.M.R. spectrum (in $CDCl_3$) of our L-N-methyl-O,O-diethylisococlaurine (**9**) with that of their synthetic sample showed a complete identity. (cf. Fig. 3: N.M.R. spectrum of our sample.)

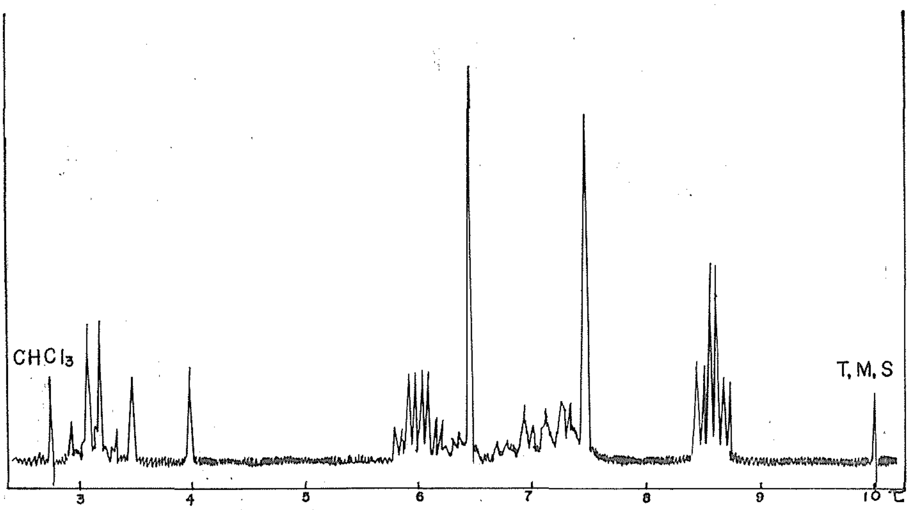
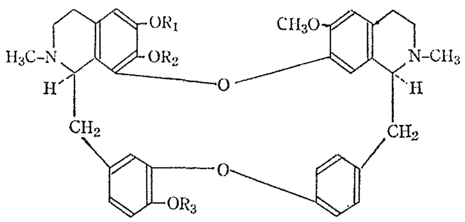


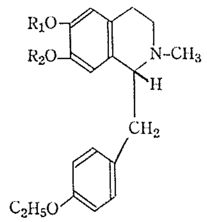

Fig. 3. Nuclear Magnetic Resonance Spectrum of L-N-Methyl-O,O-diethylisococlaurine (9). ($CDCl_3$)

Previously, Tomita and Ibuka[9] isolated an alkaloid "stepholine" from *Stephania japonica* MIERS. collected in Formosa and proposed structure **10** to this alkaloid, because they thought that the non-phenolic bisected base obtained from O,O-diethylstepholine (**11**) by cleavage with sodium in liquid ammonia was D-N-methyl-O,O-diethylisococlaurine (**12**). They reported that the oxalate of this product had m.p. 181-183° and showed $[\alpha]_D^{15}-99.3°$. The compound, however, should correspond to the antipode of L-N-methyl-O,O-diethylisococlaurine (**9**) oxalate, m.p. 146-148°, which was obtained by us.

Recently, as a result of reinvestigation on the structure of stepholine, Tomita and Ibuka[8] recognized that stepholine was obamegine (**13**) itself, and the name "stepholine" was abolished. Accordingly, the non-phenolic base which they got in the abovementioned experiments was not compound **12**, but D-N-methyl-O,O-diethylcoclaurine (**14**). Now, the sample of their oxalate, m.p. 178-180°, was compared with our oxalate, m.p. 179-180°, of the non-phenolic base which was obtained by ethylation of D-1-(4′-ethoxybenzyl)-2-methyl-6-methoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinoline (**16**), one of the phenolic basic products from the cleavage reaction by sodium in liquid ammonia of O,O-diethylaromoline (**15**). A mixed melting test confirmed their complete identity. In the previous paper[2] we recognized the slight difference between infrared spectra of both samples in nujol, and therefore, we reinvestigated the infrared spectra which were taken again in KBr and observed the complete identity as shown in Fig. 4.



10: $R_1=H$; $R_2=CH_3$; $R_3=H$
11: $R_1=C_2H_5$; $R_2=CH_3$; $R_3=C_2H_5$
13: $R_1=CH_3$; $R_2=H$; $R_3=H$



12: $R_1=C_2H_5$; $R_2=CH_3$
14: $R_1=CH_3$; $R_2=C_2H_5$
16: $R_1=CH_3$; $R_2=H$

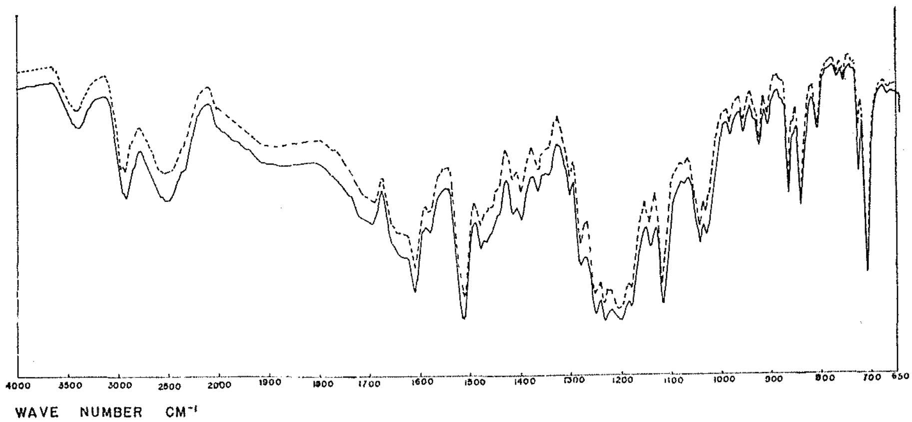



Fig. 4. I.R. Spectra (KBr)
—— Our Oxalate of Compound 14.
- - - - Ibuka's Sample of the Oxalate of Compound 14.

In order to make sure, infrared spectrum in nujol of the oxalate of the ethylated product (**14**) derived from compound **16** which was obtained from O,O-diethyl-aromoline (**15**) was compared with that of the oxalate of compound **9**. The clear

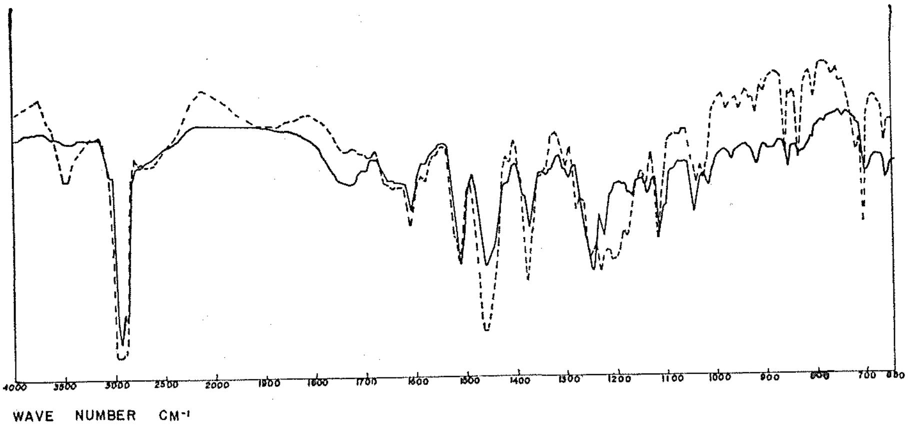



Fig. 5. I.R. Spectra (in Nujol)
—— Oxalate of Compound 9.
---- Oxalate of Compound 14.

Table 1.

| | m.p. | $[\alpha]_D$ |
|---|---|---|
| Methiodide of L-N-methylisococlaurine (**7**) | 202-204° and 221-223° (decomp.) | +8.9° (C=0.45) |
| Lotusine (**8**) iodide | 202-204° and 221-223° (decomp.) | −16.7° (C=1.2)†† |
| L-N-methyl-O,O-diethyl-isococlaurine (**9**) oxalate | 146-148° | +3.1° (C=0.65) |
| D,L-N-methyl-O,O-diethyl-isococlaurine oxalate | 174° | ±0° |
| D-N-methyl-O,O-diethyl-coclaurine (**14**) oxalate | 179-180°† | −99.3°[9)] |

† 181-183° in ref. 9). †† Information from Mr. H. Furukawa. cf. ref. 7).

difference was observed as shown in Fig. 5.

As a result of the above-mentioned experiments, it was completely established that an end of diphenyl ether linkage was attached to the position **6** of isoquinoline part in the right-hand benzylisoquinoline of O-methylthalicberine (**6**), and the various data of N-methyl-O,O-diethylcoclaurine and N-methyl-O,O-diethylisococlaurine could be explained without discrepancy. The several data of the benzylisoquinolines in question will be shown in Table 1.

## EXPERIMENTAL*3

**Methiodide of L-N-methylisococlaurine** (7). The cleavage of O-methylthalicberine with sodium in liquid ammonia was carried out in a quite same manner described in the previous paper[2)]. The phenolic cleaved base separated from non-phenolic base crystallized from acetone. The crystal of L-N-methylisococlaurine (7), m.p. 208-212°,*4 was dissolved in methanol and heated with excess

*3 All melting points are uncorrected.

of methyl iodide on a water bath for 4 hrs. The solvent and excess methyliodide were evaporated off to give a residue which crystallized from ethanol. m.p. 202-204° (decomp.). Recrystallization from ethanol after drying over anhydrous phosphoric acid in a vaccum at 70° gave a colorless needles, m.p. 221-223° (decomp.), $[\alpha]_D^{30}+8.9°$ ($c$, 0.45, MeOH). *Anal.* Calcd. for $C_{18}H_{21}NO_3 \cdot CH_3I$: C, 51.66; H, 5.48; N, 3.18. Found: C, 51.43; H, 5.64; N, 2.95. The infrared spectrum of the methiodide in KBr was superimposable with that of lotusine iodide. (See Figs. 1 and 2.)

**Oxalate of L-N-methyl-O,O-diethylisococlaurine (9).** The ethereal solution of diazoethane was added to the solution of L-N-methylisococlaurine (**7**) in methanol and allowed to stand for 24 hrs. The solvent and excess diazoethane were distilled off to give an oily residue which was chromatographed on silica gel with chloroform. The fraction which was shown to be almost homogeneous on thin layer chromatogram was again purified by column chromatography using alumina. N.M.R. spectrum in $CD\,Cl_3$ (Fig. 3.) of the benzene eluate, which proved to be homogeneous on thin layer chromatogram, was completely identical with that of D, L-N-methyl-O,O-diethylisococlaurine.

Oxalate was prepared as usual; m.p. 146-148° (from acetone), $[\alpha]_D^{32}+3.1°$ ($c$, 0.65, MeOH). *Anal.* Calcd. for $C_{22}H_{29}O_3N \cdot (CO_2H)_2$: C, 64.70; H, 7.01; N, 3.14. Found: C, 64.71, 64.50; H, 7.38, 7.12; N, 3.18.

**Identification of two oxalates.** The admixture of Ibuka's oxalate, m.p. 178-180°, and our oxalate, m.p. 179-180°, (oxalate of **14**) gave no depression of the melting point. Infrared spectra (in KBr) of both oxalates were superimposable. (Fig. 4).

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*4 cf. m.p. 217° (decomp.) in ref. 2).